**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of
Tetsuya IKEMOTO et al.
Serial No. 10/086,076 Group Art Unit 1621
Filed February 28, 2002 Examiner Michael L. Shippen
For : PRODUCTION METHOD OF CITALOPRAM, INTERMEDIATE THEREFOR AND PRODUCTION METHOD OF THE INTERMEDIATE

**TRANSLATOR'S DECLARATION**

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of the certified copy of Japanese Patent Application No. 065527/2000 filed on March 9, 2000; and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 21st day of May, 2003.

Ritsuko Arimura

(Translation)

P A T E N T  O F F I C E

J A P A N E S E  G O V E R N M E N T

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : March 9, 2000

Application Number : 065527/2000

Applicant(s) : Sumika Fine Chemicals Co., Ltd.

September 1, 2000

Commissioner, Patent Office
Kozo OIKAWA
Certificate No. 2000-3069940

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【International Classification】 C07D307/77
【Inventor】
【Address】 c/o Sumika Fine Chemicals Co., Ltd. Central Research Laboratories, 1-21, Utajima 3-chome, Nishiyodogawa-ku, Osaka-shi, Osaka, Japan
【Name】 Tetsuya Ikemoto
【Inventor】
【Address】 c/o Sumika Fine Chemicals Co., Ltd. Central Research Laboratories, 1-21, Utajima 3-chome, Nishiyodogawa-ku, Osaka-shi, Osaka, Japan
【Name】 Nobuhiro Arai
【Inventor】
【Address】 c/o Sumika Fine Chemicals Co., Ltd. Central Research Laboratories, 1-21, Utajima 3-chome, Nishiyodogawa-ku, Osaka-shi, Osaka, Japan
【Name】 Masami Igi
【Applicant】
【Identification Number】 592120519
【Name】 Sumika Fine Chemicals Co., Ltd.
【Agent】
【Identification Number】 100080791
【Patent Attorney】
【Name】 Hajime Takashima
【Telephone Number】 06-6227-1156
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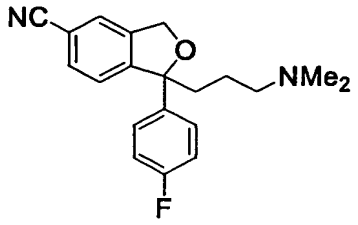
【List of the Annexed Documents】
【Document】 Specification One copy
【Document】 Abstract One copy
【Number of General Power of Attorney】 9908856
【Proof】 Requested

【Document】 Specification

【Title of the Invention】 Production Method Of Citalopram

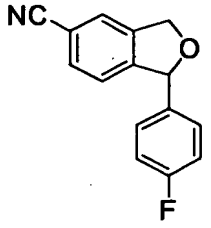
【What is Claimed is】

【Claim 1】 A production method of citalopram represented by the formula [II]



[II]

, which comprises reacting a compound of the formula [I]



[I]

with 3-dimethylaminopropyl chloride in the presence of a condensing agent and at least one member selected from N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone.

【Claim 2】 The production method of Claim 1, wherein the condensing agent is sodium hydride.

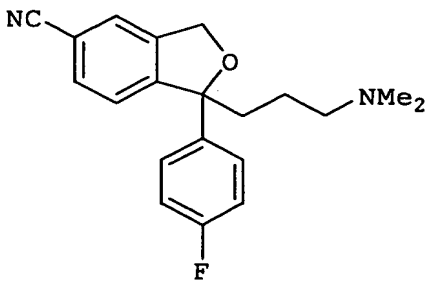
【Detailed Description of the Invention】

【Technical Field to which the Invention pertains】

The present invention relates to a production method of citalopram useful as an antidepressant.

【Prior Art】

Citalopram of the formula [II]



[II]

is useful as an antidepressant. As a production method of citalopram, for example, compound of the above formula [I] is reacted with 3-dimethylaminopropyl halide in the presence of a condensing agent (JP-B-61-35986). In the Example of this

publication, sodium hydride is used as a condensing agent. According to this method, citalopram is obtained at a low yield, and therefore, this method is not a preferable one. Moreover, this publication does not teach how to increase the yield, not to mention the use of a different additive besides the condensing agent to improve the yield.

As a different production method of citalopram, there is reported reaction of compound of the above formula [I] with 3-dimethylaminopropyl halide under basic conditions (WO98/19511). In the Example of this publication, lithium diisopropylamide obtained from n-butyllithium and diisopropylamine is used as a base. While the yield is improved, expensive n-butyllithium is used and a reaction at a very low temperature (Example, from -50°C to -40°C) is required, which makes the method industrially unpreferable. This publication does not teach an economical base that permits reaction in a typical temperature range, or industrial and economical production of citalopram at a high yield under basic conditions wherein specific bases are combined.

【Problems to be Solved by the Invention】

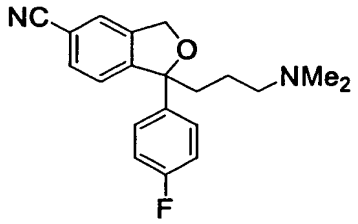
It is therefore an object of the present invention to provide an economical and industrially advantageous production method of citalopram, which affords production of citalopram at high yields.

【Means of Solving the Problems】

In an attempt to provide an economic, high yield and industrially advantageous production method of citalopram, the present inventors have conducted intensive studies of the method described in JP-B-61-35986 that utilizes a condensing agent, and found that, by further adding, besides a condensing agent, at least one of N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone, the yield of citalopram can be increased, which resulted in the completion of the present invention.

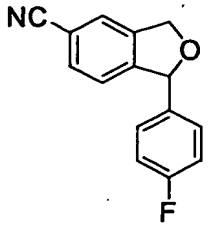
Thus, the present invention provides the following.

(1) A production method of citalopram (1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile) represented by the formula [II]




[II]

, which comprises reacting a compound (1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile; hereinafter to be also abbreviated as compound [I]) of the formula [I]




[I]

with 3-dimethylaminopropyl chloride in the presence of a condensing agent and at least one member selected from N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone.

(2) The production method of (1) above, wherein the condensing agent is sodium hydride.

【Mode of Embodiment of the Invention】

The present invention is explained in detail in the following.

Citalopram can be obtained at a high yield by reacting compound [I] with 3-dimethylaminopropyl chloride together with a condensing agent and in the presence of at least one of N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone. To be specific, compound [I], 3-dimethylaminopropyl chloride, a condensing agent, and at least one of N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone are mixed in a suitable solvent, and the mixture is heated where necessary for the progress of the reaction to give citalopram. The order of addition is subject to no particular limitation. For example, compound [I] is added to the reaction solvent, and a condensing agent and 3-dimethylaminopropyl chloride are successively added. Alternatively, compound [I] and 3-dimethylaminopropyl chloride are added to the reaction solvent, and a condensing agent is added, or a condensing agent is added to the reaction solvent, and compound [I] and 3-dimethylaminopropyl chloride are

successively added or added by mixture. In this case, N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone can be added at any stage. The reagents used in the present invention can be added as they are or added after dilution with a reaction solvent or a different solvent that does not interfere with the reaction (e.g., triethylamine, pyridine, N,N-dimethylaniline and the like). In the present invention, a quaternary ammonium salt (e.g., tetra n-butylammonium halide, benzyltrialkylammonium halide and the like) is further added in an amount of preferably 0.001 mol-0.1 mol, more preferably 0.01 mol-0.05 mol, per 1 mol of compound [I]. In this way, the reaction can be made to proceed without elevating the reaction temperature too high.

The amount of 3-dimethylaminopropyl chloride to be added is preferably 1 mol-3 mol, more preferably 1 mol-1.5 mol, per 1 mol of compound [I]. When the 3-dimethylaminopropyl chloride is in the form of a hydrochloride, it is preferably prepared into a free form by neutralization, and used for the reaction of the present invention.

The amount of N,N,N',N'-tetramethylethylenediamine to be added is preferably 0.1 mol-10 mol, more preferably 0.2 mol-4 mol, per 1 mol of compound [I].

The amount of 1,3-dimethyl-2-imidazolidinone to be added is preferably 1 mol-50 mol, more preferably 3 mol-30 mol, per 1 mol of compound [I].

The condensing agent used in the present invention is subject to no particular limitation as long as it is generally used as a condensing agent. Examples thereof include sodium hydride, potassium hydride, calcium hydride, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, potassium tert-butoxide, sodium tert-butoxide, sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, lithium diisopropylamide, lithium hexamethyldisiladide and the like, with preference given to sodium hydride and potassium tert-butoxide, with more preference given to sodium hydride. The amount of the condensing agent to be used is generally 0.9 mol-3 mol, preferably 1 mol-1.5 mol, per 1 mol of compound [I].

The reaction solvent to be used in the present invention is, for example, dimethyl sulfoxide, sulfolane, N,N-dimethylformamide,

N,N-dimethylacetamide, tetrahydrofuran (THF), 1,4-dioxane, 1,3-dioxolan, dimethoxyethane, diethylene glycol dimethyl ether, tert-butyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether, anisole, benzene, toluene, xylene, mesitylene, cyclohexane, heptane, hexane, liquid paraffin and the like, with preference given to dimethyl sulfoxide, sulforane, N,N-dimethylformamide, N,N-dimethylacetamide, tetrahydrofran, 1,3-dioxolan, dimethoxyethane, diethylene glycol dimethyl ether, toluene, xylene, tert-butyl methyl ether and liquid paraffin, which may be used alone or in combination. In addition, N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone may be used as a reaction solvent. The reaction solvent in the present invention is particularly preferably a mixed solvent of toluene and N,N,N',N'-tetramethylethylenediamine or 1,3-dimethyl-2-imidazolidinone in view of the yield.

The amount of the reaction solvent to be used in the present invention varies depending on the kind of the reaction solvent, reaction conditions and the like. It is generally preferably 1 L-100 L, more preferably 3 L-30 L, per 1 kg of compound [I].

The reaction temperature is generally from -70°C to 150°C, preferably 20°C-90°C, more preferably 40°-70°C. The reaction time is subject to no particular limitation, and is generally 30 min-15 hr, preferably 2-8 hr.

Citalopram can be isolated and purified by a conventional post-treatment and separation. For example, the reaction mixture is poured into ice water and extracted with an organic solvent. The obtained organic layer is extracted with an aqueous acid solution, neutralized and extracted again with an organic solvent, which is followed by evaporation of the solvent to isolate citalopram. Where necessary, a conventional method is used for the purification.

The starting compound [I] is, for example, synthesized according to the method of JP-B-61-35986.

【Examples】

The present invention is explained in more detail by referring to Examples. The present invention is not limited in any way by these examples.

**Example 1**

60% Sodium hydride (0.96 g) was dispersed in THF (20 ml), and to this suspension was added dropwise a solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (5.0 g) in THF (10 ml) at 40 - 50°C under a nitrogen atmosphere. Thereto was added tetra n-butylammonium bromide (0.2 g), and a solution of 3-dimethylaminopropyl chloride (3.4 g) in tert-butyl methyl ether (18 ml) was added dropwise, which was followed by stirring for 10 min. Further, 1,3-dimethyl-2-imidazolidinone (26.1 g, 25 ml) was added and the mixture was stirred at 61 - 64°C for 6 hr. The reaction mixture was poured into ice water (83 ml) and extracted 3 times with toluene (33 ml). The organic layer was extracted 3 times with 20% aqueous acetic acid (41 ml), and the obtained aqueous layer was neutralized with 25% aqueous sodium hydroxide solution (120 g) and extracted 3 times with toluene (40 ml). The obtained organic layer was washed with water, and the solvent was evaporated to give 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) as a viscous oil (5.36 g, yield 79.1%).

This oil was converted to hydrobromide by a conventional method and the obtained crystals had a melting point of 184-186°C.
$^1$H-NMR($CDCl_3$, 400 MHz) $\delta$:1.26-1.52(2H,m), 2.11-2.26(4H,m), 2.13(6H,s), 5.15(d,J=13Hz,1H), 5.19(d,J=13Hz,1H), 7.00(t,J=9Hz,2H), 7.41(d,J=8Hz,1H), 7.43(dd,J=9Hz,J=5Hz,2H), 7.50(1H,s), 7.59(1H,d,J=8Hz)ppm

HPLC retention time and measurement conditions

Retention time;10.5 min

Column; manufactured by GL Sciences, Inertsil(trademark) ODS-2 4.6 mm×150 mm

Buffer solution;0.01% aqueous trifluoroacetic acid solution

Mobile phase;acetonitrile:buffer solution=2:8 - 7:3, linear gradient is applied over 40 min

Flow rate;1 ml/min

**Example 2**

By the same reaction and post-treatment as in Example 1 except that N,N,N',N'-tetramethylethylenediamine (4.86 g) and N,N-dimethylformamide (25 ml) were successively added instead of 1,3-dimethyl-2-imidazolidinone (26.1 g, 25 ml), 1-(3-dimethyl

aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) was obtained as a viscous oil (5.13 g, yield 75.7%). Hydrobromide thereof showed the same HPLC retention time and melting point as obtained in Example 1.

**Example 3**

60% Sodium hydride (0.58 g) was dispersed in THF (12 ml), and to this suspension was added dropwise a solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (3.0 g) in THF (6 ml) at 40 - 50°C under a nitrogen atmosphere. Thereto was added tetra n-butylammonium bromide (0.12 g), and a solution of 3-dimethylaminopropyl chloride (2.0 g) in tert-butyl methyl ether (12 ml) was added dropwise, which was followed by stirring for 10 min. Further, N,N,N',N'-tetramethylethylenediamine (0.73 g) and N,N-dimethylformamide (14.2 g, 15 ml) were added and the mixture was stirred at 61 - 64°C for 7 hr. The reaction mixture was treated in the same manner as in Example 1 to give 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) as a viscous oil (3.14 g, yield 77.2%). Hydrobromide thereof showed the same HPLC retention time and melting point as obtained in Example 1.

**Example 4**

By the same reaction and post-treatment as in Example 3 except that 1,3-dimethyl-2-imidazolidinone (6.3 g, 6 ml) and N,N-dimethylformamide (8.5 g, 9 ml) were added instead of N,N,N',N'-tetramethylethylenediamine (0.73 g) and N,N-dimethylformamide (15 ml), 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) was obtained as a viscous oil (2.88 g, yield 70.7%). Hydrobromide thereof showed the same HPLC retention time and melting point as obtained in Example 1.

**Comparative Example 1**

In the same manner as in Example 1 except that the mixture was stirred as it was at 61 - 64°C for 6 hr without adding 1,3-dimethyl-2-imidazolidinone (26.1 g, 25 ml), the reaction was carried out. As a result, the reaction hardly proceeded.

**Comparative Example 2**

By the same reaction and post-treatment as in Example 1

except that N,N-dimethylformamide (23.6 g, 25 ml) was added instead of 1,3-dimethyl-2-imidazolidinone (26.1 g, 25 ml) and the mixture was stirred at 61 - 64°C for 7 hr, 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) was obtained as a viscous oil (4.12 g, yield 60.8%).

**Example 5**

60% Sodium hydride (0.58 g) was dispersed in toluene (12 ml), and to this suspension was added dropwise a solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (3.0 g) in THF (6 ml) at 40 - 50°C under a nitrogen atmosphere. Thereto was added tetra n-butylammonium bromide (0.12 g), and a solution of 3-dimethylaminopropyl chloride (2.0 g) in toluene (12 ml) was added dropwise, which was followed by stirring for 10 min. Further, N,N,N',N'-tetramethylethylenediamine (2.92 g) and dimethyl sulfoxide (15 ml) were added and the mixture was stirred at 61 - 64°C for 7 hr. The reaction mixture was treated in the same manner as in Example 1 to give 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) as a viscous oil (2.79 g, yield 68.6%). Hydrobromide thereof showed the same HPLC retention time and melting point as obtained in Example 1.

**Example 6**

Under nitrogen atmosphere, to a solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (3.0 g) in N,N-dimethylformamide (15 ml) were added tetra n-butylammonium bromide (0.12 g) and N,N,N',N'-tetramethylethylenediamine (2.92 g). Thereto was added dropwise a solution of 3-dimethylaminopropyl chloride (2.0 g) in toluene (12 ml), and then a suspension of 60% sodium hydride (0.58 g) and liquid paraffin (1.5 ml) over 1.5 hr. The mixture was stirred at 61 - 64°C for 7 hr. The reaction mixture was treated in the same manner as in Example 1 to give 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) as a viscous oil (2.69 g, yield 66.1%). Hydrobromide thereof showed the same HPLC retention time and melting point as obtained in Example 1.

**Example 7**

By the same reaction and post-treatment as in Example 6 except that dimethyl sulfoxide (15 ml) was used instead of N,N-dimethylformamide (15 ml), 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) was obtained as a viscous oil (2.68 g, yield 65.9%). Hydrobromide thereof showed the same HPLC retention time and melting point as obtained in Example 1.

**Example 8**

Under a nitrogen atmosphere, to a solution of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (9.00 g) in 1,3-dimethyl-2-imidazolidinone (54 ml) was added 60% sodium hydride (1.73 g) at room temperature. 3-Dimethylaminopropyl chloride hydrochloride (8.02 g) was neutralized with 10% aqueous sodium hydroxide solution (39 g) and extracted twice with toluene (13.5 ml). A toluene solution of 3-dimethylaminopropyl chloride (about 6.1 g) obtained by dehydrating the extract with potassium carbonate and molecular sieves 3A was added dropwise to the above-mentioned red brown 1,3-dimethyl-2-imidazolidinone solution at room temperature under a nitrogen atmosphere. Tetra n-butylammonium bromide (0.36 g) and N,N,N',N'-tetramethylethylenediamine (4.37 g) were added and the mixture was stirred at 60 - 62°C for 5 hr. The reaction mixture was poured into ice water (149 ml) and extracted 3 times with toluene (54 ml). The organic layer was extracted 3 times with 20% aqueous acetic acid (71 ml). The obtained aqueous layer was neutralized with 25% aqueous sodium hydroxide solution (210 g) and extracted 3 times with toluene (54 ml). The obtained organic layer was washed with water, and potassium carbonate (3.6 g) and silica gel (1.8 g) were added. The mixture was thoroughly stirred and filtered. The solvent was evaporated under reduced pressure to give 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram base) as a viscous oil (10.50 g, yield 86.0%). Hydrobromide thereof showed the same HPLC retention time and melting point as obtained in Example 1.

【Effect of the Invention】

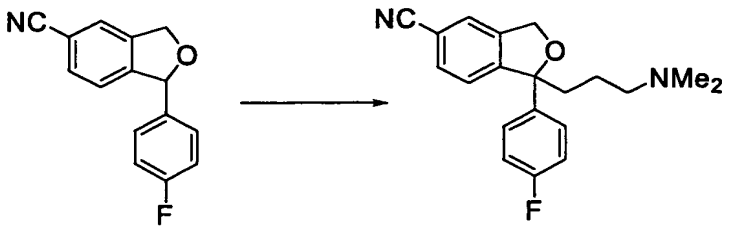
As described in the foregoing, the production method of the present invention enables industrial and economical production of citalopram, at a high yield.

【Document】 Abstract

【Abstract】

【Problem】 Provision of a production method of citalopram, which is economical, has a good yield, and which is industrially advantageous.

【Solving Means】 A compound of the following formula [I]




[I] citalopram

is reacted with 3-dimethylaminopropyl chloride in the presence of a condensing agent and at least one member selected from N,N,N',N'-tetramethylethylenediamine and 1,3-dimethyl-2-imidazolidinone.

【Main Drawing】 None